UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,856	12/06/2001	Kevin` P. Baker	GNE:2830P1C14	8365

9157 7590 07/13/2006

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER
VOGEL, NANCY S

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,856	BAKER ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-35 and 38-40 are pending in the case.

The finality of the previous Office action is hereby withdrawn.

Claim Rejections - 35 USC § 101 and 112 first paragraph

Claims 28-35 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claims are directed to isolated polypeptides having at least 80%, 85%, 980% 99% or 100% identity to the amino acid sequence of SEQ ID NO:194 with or without its signal peptide, or the amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203232, wherein the polypeptide stimulates the uptake of glucose or FFA (free fatty acid) by adipocyte cells.

The specification also discloses that PROI303 tested positive as stimulators of glucose and/or FFA (free fatty acid) uptake. The asserted utility based upon this assay result is that the polypeptide would be expected to be useful for the therapeutic treatment of disorders where either stimulation or uptake by adipocytes would be beneficial inhibition of glucose for example, obesity, diabetes, or hyper- or hypo-

insulinemia. **First**, the specification does not indicate which asserted utilities correspond specifically to glucose uptake stimulation as opposed to glucose uptake inhibition. **Second**, the specification does not indicate what, any of the utilities set forth correspond to stimulation of FFA uptake. **Third**, the actual assay result is stimulation of glucose and/or FFA uptake, three very different activities (stimulation of glucose uptake only, stimulation of FFA uptake only, and stimulation of uptake of both). Would PROI3O3 polypeptides be useful to treat hyper- insulinemia or would it be useful to treat hypo-insulinemia, two opposite conditions? **Fourth**, it is unclear how increasing uptake of FFA into adipocytes would treat obesity (or thus diabetes). Fabris et al teaches that in obesity, excessive energy storage as fat is mainly due to an imbalance between energy intake and expenditure, and the preferential channeling of excess calories as fat rather than protein or glycogen may play an important role in the development and maintenance of the disease. FFA-induced insulin resistance saves scarce glucose for central nervous system requirements, but this becomes counterproductive in obesity because it inhibits glucose utilization when there is no need to save glucose and FFA might thus be channeled toward tissues (such as adipose tissue in which insulin sensitivity is maintained or even improved) (page 601, second column). Thus, increase of uptake of FFA and/or glucose into adipocytes does not appear to be a utility for treatment of obesity or diabetes. Furthermore, the observed differences do not appear to be statistically significant and the cutoff points appear to be arbitrary and there is not obvious scientific basis for them. For example, Santomauro et al. (1999. Diabetes 48:1836-1841) teach that 56.5% decreases in FFA levels are statistically significant

and correlated with physiological improvements, but it is not clear from either the prior art or the specification whether 50% decreases are useful (see Table 2 from Santomauro et a1.). Note that 50% decreases in plasma insulin do appear to be significant, but is not clear whether this is due to a doubling of insulin uptake by adipocytes or by other tissues, or whether it is due to changes in the amount of insulin production. Similarly, the observation that 56.5% decreases in circulating FFAS is significant and correlated with physiological improvements does not indicate that a doubling of uptake of FFAS by adipocytes will lead to the same decreases in FFAS. For example, doubling the amount of FFA uptake from 1% to 2% of total circulating FFAS would not be expected to lead to a 56% decrease in circulating FFA levels. Finally, it is noted that the result of a single in vitro assay, even if it were disclosed in the specification to show that FFA uptake was enhanced by the presence of PRO1303 in the culture medium, does not provide the utility **in currently available form** of treating humans for any condition listed, i.e. obesity, diabetes, hypo- or hyper-insulinemia (page 511 of the specification). Problems such as toxicity, method of delivery to appropriate cell types, stability in the bloodstream, dosage, etc. which would affect the utility in effective treatment of complex conditions such as obesity and diabetes have not been solved, or even contemplated to be approached, by the disclosure. Bathing a cell culture of adipocytes with culture media containing some unknown concentration of the claimed polypeptide whose function is totally unknown overnight hardly rises to the level of a utility in vivo for the treatment of complex disease conditions in a human being. Rather it constitutes a preliminary, though perhaps interesting, result in a screening type

assay which would invite further experimentation before being actually useful for treatment of the conditions disclosed. 35 U.S.C. 101 specifically requires that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. Because the instant specification, as filed, fails to disclose a specific role of PRO1303 in glucose and/or FFA uptake in adipocytes, one would have reasons to conclude that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form.

In their response in the appeal brief, applicants have argued that it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents. However, this ignores the argument set forth above that the specification does not disclose that glucose uptake is affected by the PRO1303, but instead only states that glucose and/or FFA uptake is affected. Further, the agents which applicants argue have been shown to be therapeutically effective agents and which increase glucose uptake by adipocyte have been well characterized and have been shown to be useful in vivo. It is not disputed that some agents have been well studied and characterized to be useful for treating diabetes and/or diabetes using extensive experimentation and research. However, this does not show that extensive research has been performed for the PRO1303 of the instant application to show its similar utility. While other groups may have also done the same glucose/FFA assay in vitro using other compounds, and shown upon further research that their compound is useful to treat disease, this does not prove anything regarding

the instant compound. Regarding the argument that if the PRO1303 affects FFA uptake only, (which again it is emphasized, is not actually stated in the specification) this would show that the PRO1303 has utility in the treatment of obesity, diabetes and/or hyper- or hypo- insulinemia, applicant cites several publications that they argue disclose that high FFA circulating counter a trend of FFA-induced insulin resistance (pages 13-17). However, it is maintained that PRO1303 has not been shown to reduce levels of FFA in the bloodstream by increasing uptake into adipocytes, which would be required to have such an effect. Applicant argues that Fabris et al. teaches that "FFA-induced insulin resistance is a result of high circulating FFA levels (page 604, col. 2). And "this resistance leads to less utilization of glucose, which contributes to the development of obesity or diabetes" . However, applicant's argument that increasing uptake of FFA by adipocytes has the result of lowering circulating FFA levels, and thus must cause reduction in insulin-resistance, does not take into account the effect of the increased levels of FFA in adipocytes and the probable contribution this would have to obesity. Berk et al. (J. Biol. Chem. 272 (13): 8830-8835, 1997) teaches that increase FFA uptake in adipocytes is present in genetically obese rats (see abstract and discussion), suggesting that the PRO1303 would actually increase obesity. Furthermore, aside from the effect of increased intracellular FFA in adipocytes, there is no evidence that the PRO1303 protein would affect the levels of circulating FFA to the extent required to result in lowering insulin resistance, or to the extent required to result in effective treatment of diabetes, obesity, and/or hyper- or hypo-insulinemia. Regarding the argument that the results in the specification may not be statistically significant,

applicants argue that "lowering FFA levels to only normal levels (requiring a decrease of only 41-44%) would also be useful". However, it is noted that Santomauro et al. discloses results of in vivo levels of FFA, not in vitro levels as is disclosed in the instant specification. The two are not fair comparisons. Furthermore, applicants argue at page 14 of the brief that "no evidence" is provided for the assertion made by the Examiner that "the observation that 56.5% decreases in circulating FFAs is significant and correlated with physiological improvements does not mean that a doubling of uptake of FFAs by adipocytes will lead to the same decreases in FFAs". However, this "assertion" is evident on its face to the ordinary skilled artisan. One would hardly expect that concentrations of the PRO1303 found in the culture dish containing cultured adipocytes and medium during the FFA/glucose uptake assay, to be the same as concentrations of FFA circulating in the blood system of a human being when PRO1303 is somehow administered. Therefore, nothing can be said about the quantitative effect of PRO1303 on levels circulating FFA in vivo from the results shown in the specification.

Another utility asserted by the specification is based upon gene amplification data for the gene encoding the PRO1303 polypeptide in colon and lung tumor. The specification asserts that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. However, the art shows that amplification data for genomic DNA have no bearing on the utility of the encoded polypeptides. tumors, amplified genomic DNA would have to correlate with amplified

mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS In order for PR0269 polypeptides to be overexpressed in lung USA 95214717-14722), who disclose that: '1An analysis of WISP-3 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISPQ DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." See p. 14722, second paragraph of left column', pp. 14720-14721 , "Amplification and Aberrant Expression of WISPS in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a >ipgle Phl template" (see abstract). Even if increased mRNA levels could be established for PRO1303, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1 :304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and it is not possible to predict overall protein expression

levels based on average mRNA abundance in lung cancer samples" (pp. 31 1-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than I-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than so-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al.. (1999, Mol. Cell. Biol. 19:17207

1730) conducted a similar study with over 150 polypeptides. They concluded that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady- state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column). The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a poor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-1 17.8) cautions against assuming that mRNA levels are generally correlative of protein levels The reference teaches (page 1 17.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein

expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their in vivo half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 1 17.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Therefore, data pertaining to PR01303 genomic DNA do not indicate anything significant regarding the claimed PR01303 polypeptides. The data do not support the specification's assertion that PR01303 polypeptides can be used as a cancer diagnostic agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PR01303 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PR01303 polypeptide levels are also different between specific cancerous and normal tissues, the

proposed use of the PR01303 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "(i)t is not a reward for the search, but compensation for its successful conclusion."

Applicants have argued that the patentable utility of PR01303 polypeptides is based on the gene amplification data for the gene encoding the PR01303 polypeptide. Applicant states that the specification shows significant amplification of the gene encoding PR01303 in five different lung tumor samples. Appellant refers to the declaration of Dr. Goddard as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for monitoring cancer development, and/or for measuring the efficacy of cancer therapy. Appellant concludes that one of ordinary skill in the art would find it credible that the claimed PR01303 polypeptides have utility as markers for the diagnosis of lung tumors. This has been fully considered but is not found to be persuasive for the following reasons. The art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide

levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Greenbaum et al.). Since the instant claims are directed to polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection. Applicant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the amplification of the gene encoding PR01303 in five lung tumors is credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. This line of argument and the Goddard declaration are relevant to the utility of the PR01303 DNA, but not the PR01303 polypeptide. As discussed above, the art shows that increased DNA levels are not predictive of increased mRNA levels, and that increased mRNA levels are not predictive of increased polypeptide levels.

At pages18-20 of the Brief, Applicant argues that the combined teachings of Pennica et al. and Konopka et al. are not directed to genes in general but to a single gene or genes within a single family. Applicant urges that their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or polypeptide levels. Applicant argues that Omtoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification increased mRNA expression. Applicant points to the Polakis Declaration as establishing that there is a general correlation between mRNA levels and polypeptide levels. Finally, Applicant concludes that, while there may be exceptions, there is generally a good correlation between 'gene

amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PR01303 conveys utility to the claimed PR01303 polypeptides. This has been fully considered but is not found to be persuasive. While Pennica et al. and Konopka et al. are directed to small numbers of genes, the instant application concerns only one gene as well. Furthermore, Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., LaBaer, and Greenbaum et al. all speak to larger sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. Regarding the Polakis Declaration, Applicant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant concludes that all of the submitted evidence support Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature

of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PR01303 (i.e., data regarding amplification of PR01303 genomic DNA), and does not disclose any information regarding PR01303 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 170/c of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al., all discussed supra. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts, however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

At p. 24 of the Brief, Applicant argues that, even if there were no correlation

between gene amplification and increased mRNA/polypeptide expression, a polypeptide encoded by a gene that is amplified in cancer would still have utility in that simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification, leading to a better determination of a suitable therapy, as demonstrated by the real-world example of the breast cancer marker HER-2/neu. Appellant points to the Ashkenazi declaration as supporting this point. This has been fully considered but is not found to be persuasive, since the specification does not disclose that the PR01303 polypeptide levels increase or stay the same. Further research would be needed to reasonably confirm whether or not there is a change in PR01303 polypeptide levels in cancers showing gene amplification of PR01303 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PR01303 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides.

Regarding the declaration of Dr. Ashkenazi, Dr. Ashkenazi states that, if gene amplification results in over-expression of the mRNA and corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Applicant concludes that the examiner has not shown a lack of correlation between gene amplification data and the biological significance of cancer genes. Applicant urges that a credible, specific, and substantial asserted utility has been established for PR01303 polypeptide. This has been fully considered but is not found to be persuasive. There is no evidence of record that

PR01303 polypeptide is expressed at elevated levels in cancer tissue. The specification indicates that PR01303 genomic DNA is amplified in several lung tumor samples. However, this is not predictive of elevated PR01303 polypeptide levels in view of the state of the art which establishes that it is more likely than not that amplified DNA levels fail to correlate with increased mRNA (transcript) levels, and that elevated mRNA levels fail to correlate with elevated polypeptide levels. See Pennica et al., Konopka et al., Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et àl., and Greenbaum et al. From p. 24-25 of the Brief, Applicant points to the declaration of Dr..Ashkenazi as establishing that, even if the protein were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification. Applicant concludes that such a situation would allow for better tumor classification and better determination of suitable therapy. Applicant argues that absence of overexpression is crucial information for a clinician, because it indicates that the patient should not be treated with agents that target that gene product. Applicant argues that this saves money and benefits the patients who can avoid exposure to the side effects associated with such agent. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PR01303 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention' are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PR01303

polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1303. For example, neither the specification nor the prior art discloses an agent that targets PR01303 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At pp. 6-7 of the Brief, Applicant argues that, since PR01303 polypeptides have utility in the diagnosis of cancer, they are also enabled. Appellant also argues that the skilled artisan would know how to use the claimed polypeptides in treatment of disorders for which "modulation of glucose uptake by adipocytes would be beneficial, such as obesity, diabetes, and hyper- or hypo- insulinema" and also in cancer diagnosis based on the disclosure. This has been fully considered but is not found to be persuasive since the PR01303 polypeptides have no utility for the reasons set forth in the rejection under 35 U.S.C. 101, above, they also are not enabled.

35 U.S.C. 112, first paragraph, enablement

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-32 and 39-40 would remain rejected under 35 U.S.C. 112, first paragraph.

The specification teaches that the term "PRO/number polypeptide' and PRO/number' wherein the term 'number' is provided as an actual numerical designation

as used herein encompass native sequence polypeptides and polypeptide variants (pg 301, lines 1-6). The PRO1330 nucleic acids and polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods (pg 301, lines 6-8). The specification discloses that a PRO polypeptide variant is defined as an active PRO polypeptide having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence, a full-length native sequence PRO polypeptide sequence lacking the signal peptide, an extracellular domain of a PRO polypeptide, with or without signal peptide, or any other fragment of a full-length PRO polypeptide sequence (pg 302, lines 4-32). However, the specification does not teach any variant, fragment, or derivative of the PRO1303 polypeptide other than the full-length amino acid sequence of SEQ ID NO: 194. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives recited in the claims. The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may

also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et a1., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues', therefore substitution of non-essential residues can even destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et 2., 2000, Trends in Biotech. 1841):34-39, especially p. 36 at Box 2; Doerks et 2., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, NatureBiotechnology 15: 1222-1223; Brenner, 1999, Trends in Genetics 15: 132-133; Bork d a1., 1996 Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of

the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 US. C. ll2 first paragraph (Written Description)

Claims 28-32 and 39-40 are rejected under 35 U.S.C. 1 12, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, claims 28-32 and 39-40 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide of SEQ ID NO: 194, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the CDNA deposited under ATCC accession number 203232; wherein the polypeptide increases the uptake of glucose or FFA by adipocyte cells. The claims recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity and a function wherein the polypeptide increases the uptake of glucose or FFA by adipocyte cells. There is not even identification of any particular portion of the structure that must be conserved or that the described function is truly representative of all members of the claimed genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polypeptide species (SEQ ID NO: 194) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments and with at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide comprising the amino acid sequence of SEQ ID NO: 194.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description' inquiry, whatever is now claimed" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed" (See Vas-cath at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description

requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481at 1483. In Fiddes, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 194 , but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph.

Appellant is reminded that Vas-cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NV
7/8/06

NANCY VOGEL
PRIMARY EXAMINER